Brain, Behavior, and Immunity 125 (2025) 58–67

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

COVID-19 may Enduringly Impact Cognitive Performance and Brain Haemodynamics in Undergraduate Students

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ARTICLE INFO

Keywords:
SARS-CoV-2
Haemodynamic Response
Cognitive Functioning
NIRS
Brain Fog
Young Adults
Long COVID
Post-COVID
Cognition

ABSTRACT

To date, 770 million people worldwide have contracted COVID-19, with many reporting long-term "brain fog". Concerningly, young adults are both overrepresented in COVID-19 infection rates and may be especially vulnerable to prolonged cognitive impairments following infection. This calls for focused research on this population to better understand the mechanisms underlying cognitive impairment post-COVID-19. Addressing gaps in the literature, the current study investigated differences in neuropsychological performance and cerebral haemodynamic activity following COVID-19 infection in undergraduate students. 94 undergraduates (age in years: $M = 20.58$, $SD = 3.33$, range = 18 to 46; 89 % female) at the University of Otago reported their COVID-19 infection history before completing a neuropsychological battery while wearing a multichannel near-infrared spectroscopy (NIRS) device to record prefrontal haemodynamics. We observed that 40 % retrospectively self-reported cognitive impairment (brain fog) due to COVID-19 and 37 % exhibited objective evidence of cognitive impairment (assessed via computerised testing), with some suggestion that executive functioning may have been particularly affected; however, group-level analyses indicated preserved cognitive performance post COVID-19, which may in part reflect varying compensatory abilities. The NIRS data revealed novel evidence that previously infected students exhibited distinct prefrontal haemodynamic patterns during cognitive engagement, reminiscent of those observed in adults four decades older, and this appeared to be especially true if they reported experiencing brain fog due to COVID-19. These results provide new insights into the potential neuropathogenic mechanisms influencing cognitive impairment following COVID-19.

1. Introduction

In December 2019, a novel coronavirus arose with an ability for interpersonal transmission and a severe acute respiratory attack (Adedoyin & Soykan, 2023). As of December 2023, this virus, named COVID-19, had infected over 770 million and killed nearly seven million people worldwide (Mathieu et al., 2023). Post-infection, long-term COVID-19 symptoms have emerged, notably including subjective cognitive complaints/brain fog (Hugon et al., 2022). Despite being less at risk for severe acute symptoms (Kapusta et al., 2023), young adults recently recovered from COVID-19 have a high prevalence of subjective and objective cognitive impairment (17 %-85 %) (Herrera et al., 2023; Mogensen et al., 2023). This is concerning given that university/college campuses have been identified as "superspreader" sites (Lu et al., 2021), contributing to the overrepresentation of young adults in infection rates globally (World Health Organisation, 2023).

2. COVID-19 and prolonged cognitive impairment

Initial concerns regarding cognitive effects of COVID-19 infection were based on cognitive impairments associated with other respiratory illnesses. Observational studies have revealed cognitive impairments after influenza (Talarowska et al., 2011), acute respiratory distress syndrome (Jackson et al., 2009), the common cold (Smith, 2012), chronic obstructive pulmonary disease (Ranzini et al., 2020), and various other upper respiratory infections (Vickers & Hervig, 1989). With these illnesses, cognitive function is broadly impaired (including information processing, attention and concentration, declarative

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https://doi.org/10.1016/j.bbi.2024.12.002
Received 12 May 2024; Received in revised form 19 November 2024; Accepted 9 December 2024
Available online 19 December 2024
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memory, executive functioning, and self-control) (Cleutjens et al., 2014; Talarowska et al., 2011). Among recovered COVID-19 patients, complaints have emerged pertaining to persistent difficulties with attention/concentration, disorientation, and lethargy (symptoms collectively referred to as brain fog), which signalled that COVID-19 may also have long-term cognitive effects (McCorkell et al., 2021).

This evidence sparked research studies undertaking objective testing for cognitive impairments following COVID-19 infection. Firstly, Zhou et al. (2020) found selective attention deficits (but no difference in visual perception or memory abilities) in recovered hospitalised patients (mean age 47 years, $SD = 11$). Additionally, Hampshire et al. (2021) observed lower cognitive scores on the Great British Intelligence Test in adults following mild to severe COVID-19 (mean age 47 years, $SD = 16$), and Raman et al. (2021) found executive and visuospatial deficits 2–3 months post-infection in older adult COVID-19 patients post-hospital discharge (mean age 55 years, $SD = 13$). Concerningly, in non-hospitalised adults following COVID-19 infection, cognitive impairment has been found to be associated with younger age (Henneghan et al., 2022), and when compared to middle-aged or older recovered COVID-19 patients, young patients (aged 26–39 years) displayed larger impairments in working memory, processing speed and executive functioning (Herrera et al., 2023). Although the impaired cognitive domains vary between studies, this evidence indicates that undergraduate students may be susceptible to adverse cognitive effects following COVID-19.

2.1. Neuropathogenesis of cognitive impairment post COVID-19

Several theories have been proposed for the pathogenesis of cognitive impairment following COVID-19 infection. Observations of chronic neuroinflammation such as astrocyte hyperactivation, cerebral hypoperfusion and tau protein accumulation has led to various hypotheses behind the cause of cognitive impairment (Aghajani Mir, 2023; Nouraeinejad, 2023). Astrocytes are glial cells that play critical roles in modulating the blood brain barrier, waste removal (Reddy & van der Werf, 2020), and synaptic transmission and plasticity (Liu et al., 2020). The SARS-COV-2 virus has been observed to cross the blood–brain barrier bound to ACE2 receptors of the hypothalamus and cause persistent mitochondrial dysfunction in microglial cells (Aghajani Mir, 2023). Implicated in neurodegeneration and brain ageing, microglia interact with astrocytes and are tasked with mediating neuroinflammation, controlling synaptic strength of neuronal networks, phagocytosis (cellular digestion of pathogens and debris) and brain injury repair (Colonna & Butovsky, 2017). According to theory, following COVID-19 infection, microglia are hyperactivated to compensate for the increased energy supply demands from dysfunctional mitochondria, driving greater oxygen demand and cerebral hypoxic stress (Aghajani Mir, 2023). Of further consequence of this hyperactivation, the SARS-COV-2 virus has been found to upregulate microglial and astrocyte production of reactive oxygen species and proinflammatory cytokines leading to chronic neuroinflammation and cell death due to excessive phagocytosis (Aghajani Mir, 2023), which is the theorised cause of persistent cognitive impairment.

Although primarily interpreted as a proxy measure of neural activity (Ayaz et al., 2019), near-infrared spectroscopy (NIRS) may also offer indirect insights into microglial activation (Yang & Dunn, 2015), potentially shedding light on the microglial hyperactivation theory (Aghajani Mir, 2023). With NIRS, neural/microglial activity is inferred by indexing changes in the oxygenated (Δoxy-Hb), deoxygenated (Δdeoxy-Hb), and total (Δtotal-Hb) haemoglobin concentrations in circumscribed cortical regions. Cerebral haemodynamic changes are regulated by our neuro-glial-vascular unit systems (Brezzo et al., 2020), so a more positive/less negative task-related change in oxygenated haemodynamic response (from baseline) suggests comparatively greater brain activation, including both neuronal and microglial activation (Ayaz et al., 2019; Brezzo et al., 2020; Yang & Dunn, 2015). NIRS has previously been proposed as a quick detection measure for COVID-19 (Assi et al., 2022; Raypah et al., 2022), and has been utilised to identify concerningly low cerebral blood oxygen saturation in hospital admitted COVID-19 patients (Battaglini et al., 2023). Furthermore, researchers have used NIRS to investigate the neurological mechanisms behind olfactory (Ho et al., 2021) and taste dysfunction symptoms following COVID-19 (Jezierska et al., 2023). However, no published studies have utilised NIRS as a measure for how the haemodynamic response to cognitive tasks may change post COVID-19 infection.

2.2. Current study

In light of the findings and proposed theories reviewed in the preceding subsections, the current study investigated whether past COVID-19 infections influence cognitive performance and the task-related haemodynamic response of undergraduate students. We focused on the far anterior prefrontal cortex underlying the forehead for NIRS recordings, due to the lack of hair enabling better signal quality (Orihuela-Espina et al., 2010; Yamada et al., 2017). Past research using NIRS recordings over these prefrontal sites in healthy (primarily young adult) undergraduates during completion of some of the same cognitive tests used in the current study found negative change values (Bierre et al., 2017; Cameron et al., 2015). With this in mind, it was hypothesised that those with a past COVID-19 infection, in comparison to those without, would exhibit impaired cognitive performance and less negative changes in oxygenated haemoglobin concentrations (measured from the forehead overlying far anterior prefrontal cortex) while completing the cognitive tasks. This would be consistent with comparatively greater prefrontal neural (Ayaz et al., 2019) and microglial activation (Yang & Dunn, 2015) during cognitive testing following recovery from COVID-19 infection.

3. Method

The study was approved by the University of Otago Human Ethics Committee (reference code 22/020) and data collection occurred from 17/04/2023 to 08/06/2023. Each participant was given an information sheet, provided verbal and written consent and informed that only anonymous group data would be reported.

3.1. Participants

94 undergraduates from the University of Otago participated in association with a psychology course. Participants all met, based on self-report, the following inclusion criteria: 18 + years old, normal or corrected to normal vision, and no psychological or neurological conditions. Participants ranged in age from 18 to 46 years ($M = 20.58$, $SD = 3.33$), and identified as female ($n = 83$) or male ($n = 11$). Regarding ethnicity, participants selected New Zealand (NZ) European ($n = 77$), Māori ($n = 8$), Chinese ($n = 3$), Indian ($n = 3$), Fijian ($n = 3$), and other ($n = 12$); note that multiple options could be selected. Participants were categorised into a covid group ($n = 75$) if they self-reported at least one past COVID-19 infection (biologically confirmed via a positive Rapid Antigen or Polymerase chain reaction test result), else they were categorised into a non-covid group ($n = 19$). Prior to completing a neuropsychological battery, participants who reported being infected with COVID-19 were asked when, how many times, if any complications arose, if they experienced brain fog (subjective cognitive impairment) and if their physical activity levels had changed since infection.

3.2. Session overview

Following initial data collection related to demographics, physical activity habits (NZPAQ-SF; Mclean & Tobias, 2004), and COVID-19 history via written questionnaires, participants completed a broad neuropsychological testing battery while wearing a multichannel NIRS

device to record prefrontal haemodynamics. The total duration of the session was 1 h, including approximately 20 min of cognitive testing.

4. Measures

4.1. Neuropsychological testing measures

The computerised battery of psychometric tests (programmed in MATLAB R2019a, The MathWorks, Natick, MA), which has been reported previously (Forsyth et al., 2016), included six visual analogue mood scales (VAMS) and eight cognitive tests (Pro, Anti, Pro/Anti, Simon, 2-back, Flanker, and Forward and Backward Spatial tasks, always completed in this order to avoid variability between individuals) designed to tap a variety of cognitive functions. For Pro, Anti, Pro/Anti, Simon, and Flanker, the dependent variable of interest was correct reaction time (ms), and all variables were equally probable and counterbalanced across the trials in a pre-randomised fixed order (to avoid variability between participants). Furthermore, for these tests, and 2-back, a 900 Hz error tone sounded for 300 ms if the wrong button was pressed, a button was pressed within 100 ms of the stimulus, or the correct button was not pressed within the allowed time frame.

Visual Analogue Mood Scales (VAMS). For each scale ('sad', 'energetic', 'tense', 'happy', 'tired' and 'calm'), participants clicked on a 100 mm horizontal line to indicate how they were currently feeling; scores could range from 0 (not at all) to 100 (extremely). A 2 cm vertical line appeared at the position on the horizontal line where the mouse was clicked and the position could be changed before pressing 'DONE'. The scales used in the current study have been demonstrated to show sensitivity to group differences in undergraduate students (Machado et al., 2019).

Pro, Anti, and Pro/Anti. The Pro, Anti, and Pro/Anti tasks were chosen to assess basic visuomotor performance, inhibitory control, and task-switching ability, respectively (Brett & Machado, 2017). Participants used their index fingers to press the left or right button (each 2 cmˆ2, with 2 cm between them) on a DirectIN Response Box (Empirisoft, New York, NY). They were instructed to look at the central white fixation dot and respond to an appearing green (same side press) or red (opposite side press) square as quickly as possible without sacrificing accuracy. The square appeared 8 degrees of visual angle to the left or right of the fixation point following a varied duration of 400, 800, 1000, or 1200 ms. The Pro task only had green squares, the Anti task only red squares, and the Pro/Anti task had both red and green squares in random order.

Simon. The Simon task was completed to measure selective attention (White et al., 2020). Participants were asked to focus at the start of each trial on a central white fixation point for a variable period (400, 800, 1000, or 1200 ms), after which a 'C' or 'T' appeared 3 degrees to the left or right. The left button on the DirectIN Response Box was to be pressed when a 'C' appeared, and the right when a 'T' appeared. Responses were separated for spatially compatible (C appearing on left or T on right) and incompatible (C on right or T on left) trials.

2-back. To test identity-based working memory, participants were asked to focus on the centre of the screen where a fixed series of 90 white uppercase 40-point Arial font consonants (not including W, Y or Z) were presented individually. Each consonant was displayed for 500 ms with a 2500 ms delay, allowing a 3000 ms response window. Participants were asked to press the left button if the displayed consonant matched the consonant two back in the series, and the right button if not, and responses were recorded for each letter shown (after the second letter). Within the series, 30 consonants matched the two-back consonant, while out of 60 unmatched consonants, three matched the one-back and three the three-back consonants. In this task, the dependent variable was the number of correct responses.

Flanker. The Flanker task, which has good convergent and discriminant validity (Zelazo et al., 2014), was designed to measure selective attention ability using the same fixation periods and stimulus–response mappings as the Simon task. However, the target consonant requiring response appeared at centre whilst flanked directly above or below (with one degree of visual angle separation) by a 'C' or 'T', which served as a distracting consonant. Responses were separated based on whether the two letters were the same (compatible) or different (incompatible).

Forward and Backward Spatial. To assess visuospatial working memory, we used a computerised version of the Corsi Block Tapping task (Corsi, 1972). Nine 3.2 cm x 3.0 cm grey boxes were displayed on the screen, in predetermined positions (based on Kessels et al., 2000). After a 500 ms delay, a preset order of boxes sequentially turned white for 1000 ms with no interstimulus interval and a tone of 400 Hz sounded for 300 ms after the final box in that sequence, signalling participants to respond. Participants were instructed to use a computer mouse to click on the boxes in the correct order they turned white (forward task) and in the opposite order (backward task). There were two sequences of every length beginning with two and up to all nine boxes (for sequence details, see Table S1 in Nasrollahi et al., 2024). The score was the product of the length of the longest correctly recalled sequence (up until they responded incorrectly to both sequences of a given length) and the number of correctly recalled sequences.

NIRS Recording Device. The Brite NIRS device was used to non-invasively measure relative concentrations of oxygenated and deoxygenated haemoglobin as task-related changes from resting baseline (Artinis-Medical-Systems, 2022). Brite is a Bluetooth device that attaches to a neoprene head cap and works with OxySoft software to store, process and display NIRS optode data. Oxysoft ran calculations of the oxygenated (oxy-Hb), deoxygenated (deoxy-Hb), and total haemoglobin (total-Hb) concentrations sampled at a rate of 10 Hz between transmitter and receiver pairs placed 3 cm apart (note that the sampled tissue lies in an elliptical arc between the transmitter and receiver optodes). Brite is a continuous wave spectrometer. We recorded a 2 min resting baseline before and after the neuropsychological battery and averaged the final minute of each for the baseline value. Reported values were the difference between this baseline and the mean value recorded during each of the cognitive tests.

4.2. Procedure

All participants completed the neuropsychological battery while we continuously recorded NIRS. The monitor used for the battery was time synced to the laptop running Oxysoft. Participants and experimenters switched all devices to flight mode before entering the body-protected testing room set up to AS/NZS 3003 standards, and metal-containing items were removed including watches, earrings, cell phones, pagers, laptops, wigs/hair pieces and rings. Once seated, participants were asked if the experimenter could touch their head and the cap was set up. They adjusted their seat height to rest their heads on a chin rest (positioned 57 cm from the monitor) and head dimensions were measured with a tape measure. Distance A (pre-auriculars) and distance B (nasion-inion) were calculated. The cap was flipped inside-out and the front centre hole was aligned with a point B/10 mm directly above the nasion, and the top middle hole was aligned with the intersection of A/2 and B/2. Cap alignment was rechecked with a tape measure and adjusted if needed. The Brite device was then attached to the cap and the blunt end of a skewer was used to move any hair before attaching the optodes (see configuration in Fig. 1).

Verbal consent was acquired to turn Brite on and connect to the Oxysoft software using Bluetooth. A 2 min baseline was then recorded; the participant was asked to sit as still as possible, rest their chin on the chin rest, and blink/breathe naturally while staring at the blank monitor.

Once setup was complete, the participant was notified that they could take breaks at any point between tests, the monitor was turned on and the six VAMS were answered successively. Prior to each cognitive task, participants were given visual and verbal instructions and

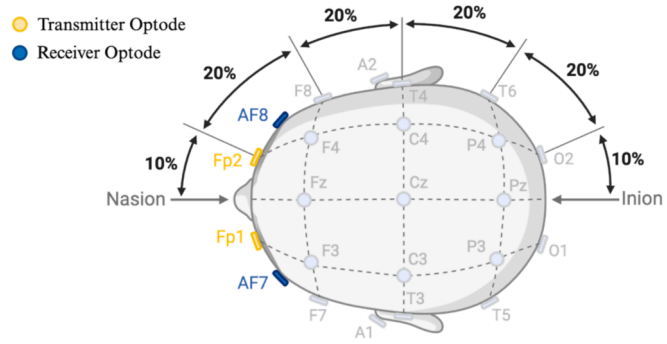

Fig. 1. NIRS channel optode positions.

completed a small series of practice trials. Participants completed: Pro (four practice trials followed by 40 test trials), Anti (four practice and 40 test trials), Pro/anti (six practice and 40 test trials), Simon (six practice and 60 test trials), 2-back (15 practice and 90 test consonants), Flanker (10 practice and 40 test trials), Forward Spatial (two, two-box practice and 16 test sequences), and Backward Spatial (two, two-box practice and 16 test sequences). Upon completion, a final 2 min baseline of NIRS recordings was taken using the same protocol as the first baseline.

4.3. Data analysis

Power analyses were conducted in R for cognitive performance differences based on the large differences ($d = 0.805$) observed by Zhou et al. (2020) between hospitalised patients with and without a past COVID-19 infection in parts two and three of the Continuous Performance Test. These tests were selected for power analysis given their similarities to the Simon, Flanker and 2-back tasks, and the lack of case-control comparisons made in past literature of a more similar sampled population to the current study. Given the current study's participant ratio between the covid and non-covid groups (3.94:1) and significance level ($\alpha = 0.05$), to reach 80 % statistical power ($1 - \beta = 0.80$), minimum group size was 55 covid and 14 non-covid participants. Regarding the NIRS variables, the current study is the first to date to analyse task-related brain haemodynamic differences between people with and without a past COVID-19 infection using NIRS. Consequently, power analyses for brain haemodynamic differences were based on findings that 65–96 % of COVID-19 patients (from various populations) exhibit EEG abnormalities (Antony & Haneef, 2020; Furlanis et al., 2023; Kubota et al., 2021). To allow 80 % statistical power ($1 - \beta = 0.80$), we took the smallest previously observed proportion of EEG abnormalities (65 %), our group enrolment ratio (3.94:1) and conservative estimates (derived from prior research) of a null proportion (20 %) of non-specific EEG abnormalities in healthy controls (Panayiotopoulos, 2005), to calculate a minimum required group size of 43 covid and 11 non-covid participants.

Cognitive performance data were cleaned by discarding participants with < 60 % accuracy ($n = 9$ for 2-back task) and forward/backward spatial scores of 0 ($n = 2$ forward, $n = 2$ backward). Furthermore, the Dixon Outlier (Q) test ($\alpha = 0.05$) was used to detect outliers, resulting in the removal of one participant's cognitive data for pro/anti reaction time. To analyse cognitive impairment at an individual level of analysis, objective cognitive impairment was defined as a score that was 1.5 standard deviations or more below the normative non-covid group mean on one or more cognitive tests. This was an established definition of impairment that was either in line with or more conservative than prior studies (Henneghan et al., 2022; Herrera et al., 2023; Jaywant et al., 2021; Miskowiak et al., 2021). For group-level analysis, independent samples, one-tailed student and Bayesian *t* tests were utilised. However, as all cognitive dependent variables were found to be non-normally distributed in the covid group by a Shapiro-Wilk test (Table S1), Mann-Whitney U tests were also used to analyse group cognitive differences. This non-parametric test was chosen as it can compare non-normally distributed groups of different sizes. As the parametric and non-parametric tests produced the same patterns of results, we chose to report only the parametric test results in the text; see the supplementary materials for the non-parametric test results (Table S2).

NIRS data were high and low pass filtered to remove substantial artifacts, and the NIRS parameters (Δoxy-Hb, Δdeoxy-Hb, and Δtotal-Hb) were calculated for each cognitive test, for each participant. The resulting analysed parameters were the task-related changes from baseline. To test for haemodynamic differences between groups, a three-way MANOVA was used. Q-Q plots were analysed and the Shapiro-Wilk test was applied and found non-normality of all dependent variables (Tables S3, S4 and S5, Figs. S1, S2 and S3). NIRS variables were transformed using Lambert W x Gaussian transformation in R to choose the optimal transformation expression for each variable. The MANOVA was run for each of the transformed and untransformed datasets, resulting in identical statistical inferences. Consequently, to aid interpretation, results from the untransformed data are reported in the text and results from the transformed data can be found in Table S6.

Mood Scales were compared between covid and non-covid groups using independent samples, two-tailed student and Bayesian *t* tests. In validation of *t* test and MANOVA assumptions of homoscedasticity, Levene's test for Equality of Variances found no evidence of unequal variance between covid and non-covid groups in cognitive, mood, or haemodynamic variables (Tables S7, S8, S9 and S10).

5. Results

5.1. Participant characteristics

As can be seen in Table 1, Kruskal-Wallis rank sum non-parametric tests (with adjustment for tied ranks) revealed no differences in any of the listed participant characteristics between the non-covid and covid groups ($p > 0.05$ in all cases). Notably, there was one unexpectedly older participant in the non-covid group (*age* = 46), whereas all other participants were young adults (18–31 years old). Although not part of the planned analyses, given the known declines in cognitive functioning with adult ageing (Kouwenhoven & Machado, 2024; Murman, 2015) and suggested age-related differences in cognitive effects of COVID-19 infection (Herrera et al., 2023), the following analyses between covid groups were retested with exclusion of this participant, resulting in identical statistical inferences (see Table S11).

5.2. Neuropsychological performance

Table 2 shows that for each cognitive test, performance differences between covid and non-covid groups were not statistically significant. However, when participants in the covid group were analysed at an individual level, the frequency of objective cognitive impairment (defined as a score that was at least 1.5 standard deviations below the non-covid group mean) in at least one of the cognitive tasks was 37.33 %. Impairment was most prevalent in the anti and pro/anti tasks selected to measure inhibitory control and task switching abilities respectively as core executive functions. Additionally, anecdotal evidence (as inferred by $1 < BF_{10} < 3$) suggests that more recently infected participants had a greater tendency to exhibit objective cognitive impairment ($p = 0.095$, $BF_{10} = 1.565$). Furthermore, of the participants in the covid group, 40 % ($n = 30$) reported experiencing brain fog due to COVID-19 (subjective cognitive impairment). Although those reporting subjective cognitive impairment ($n = 30$) performed numerically worse than those reporting no subjective cognitive impairment ($n = 45$) on all of the cognitive measures except backward spatial score, follow-up analyses (albeit underpowered) showed no significant subgroup differences (see Table S12). As expected, for the speeded tasks in which participants were asked to avoid sacrificing accuracy (all except 2-back

Table 1
Relevant Participant Characteristics (n = 94).

	Non-Covid (n = 19)			Covid (n = 75)			Kruskal-Wallis Rank Sum Test	
Variable	**M**	**SD**	**Range**	**M**	**SD**	**Range**	**H**	**p-value**
Age (years)	21	6	18–46	20	2	18–31	0.017	0.895
Female (%)	79	NA	NA	91	NA	NA	−1.420	0.156
Education (years)	14	1	13–16	15	1	13–17	1.545	0.214
Height (m)	1.70	0.08	1.57–1.87	1.69	0.08	1.51–1.89	0.278	0.598
Weight (kg)	73.9	16.7	48–104	66.9	11.8	47–108	2.761	0.097
BMI (kg/m2)	25.7	6.1	18.3–39.4	23.4	3.2	18.3–35.5	1.396	0.237
Times Infected	0	0	0	1.5	0.6	1–3	NA	NA
Time Since Infection (months)	NA	NA	NA	10.1	4.8	1.8–17.2	NA	NA
Caffeine Consumption (%)	47	NA	NA	50	NA	NA	−0.465	0.642
Right Handed (%)	79	NA	NA	81	NA	NA	−0.236	0.810
Walking (min)	164	119	0–420	238	202	0–1080	1.784	0.182
Moderate PA (min)	148	289	0–1260	154	169	0–720	0.003	0.958
Vigorous PA (min)	125	184	0–630	119	144	0–630	0.159	0.690
Total PA (min)	437	346	0–1362	510	330	0–1500	1.139	0.286
Frequency of Activity (days/week)	3.9	2.4	0–7	4.6	2.0	0–7	1.252	0.263
Chronic PA (1–5)	4.1	1.1	1–5	4.1	1.0	2–5	0.001	0.979

Note. Sampled population was year one and two undergraduate psychology students; df = 1; M = Mean; SD = Standard Deviation; PA = Physical Activity; NA = Not Applicable; Caffeine Consumption refers to the last 12 h; Chronic PA scores refer to the self-reported state of change of their physical activity habits, where a 1 represents inactivity and no desire to change, and a 5 represents high PA for > 6 months; Group differences in Female (%), Right Handed (%), and Caffeine Consumption (%) were tested using a two-tailed Z-test to compare proportions.

Table 2
COVID-19 Differences in Cognitive Performance.

	Non-Covid (n = 19)			Covid (n = 75)			Difference		Impaired
	M	SD	95 % CI	M	SD	95 % CI	p-value	BF_{10}	%
Pro Reaction Time (ms)	326	53	302–350	310	40	301–319	0.924	0.147	4.0
Anti Reaction Time (ms)	374	47	352–395	377	55	364–389	0.414	0.299	13.3
Pro/Anti Reaction Time (ms)	546	82	510–583	553^{1}	101	530–576	0.389	0.310	13.3
Simon Overall Reaction Time (ms)	509	70	478–541	488	75	471–505	0.863	0.164	6.7
Simon Compatible Reaction Time (ms)	488	67	458–518	510	77	492–527	0.128	0.328	10.7
Simon Incompatible Reaction Time (ms)	534	71	502–566	514	73	497–530	0.865	0.151	6.7
Flanker Overall Reaction Time (ms)	525	85	487–563	520	91	500–540	0.579	0.242	8.0
Flanker Compatible Reaction Time (ms)	508	79	472–543	502	87	482–521	0.604	0.267	9.3
Flanker Incompatible Reaction Time (ms)	541	96	498–584	538	99	516–561	0.545	0.170	6.7
2-Back Correct Responses	73	6	70–76	72^{9}	7	70–73	0.159	0.493	10.6
Forward Spatial Score	58^{1}	27	46–71	60^{1}	23	55–65	0.615	0.177	0.0
Backward Spatial Score	67	32	53–82	58^{3}	19	54–63	0.060	0.657	2.8

Note. M = Mean; SD = Standard Deviation; ^{n} = reduced group sample size by n.

and forward and backward spatial), both groups achieved greater than 94 % accuracy in each task (see Table S13), consistent with the ceiling accuracy reported previously (White et al., 2022).

Table 3 shows that participants in the covid group scored significantly higher on ratings of tense mood, and there was anecdotal evidence that they were also less calm. No other mood differences were observed between groups.

5.3. Prefrontal haemodynamic response

Table 4 summarises the results of the three-way MANOVA indicating main effects and interactions between COVID-19 group, prefrontal hemisphere, and cognitive task. There was a significant main effect of COVID-19 group, consistent for all three NIRS dependent variables, where participants with a past COVID-19 infection displayed a less negative prefrontal change in oxy-Hb, deoxy-Hb, and total-Hb, on average across cognitive tasks and hemispheres (see Fig. 2). This main effect was qualified by an interaction effect with hemisphere (see Fig. 3), which is followed up in the next paragraph. Although main effects emerged for hemisphere and cognitive task, the effect of COVID-19 on prefrontal haemodynamic response did not vary across the cognitive tasks (as evidenced by the lack of significant Covid x Task interactions), and the Covid x Hemisphere interaction did not significantly differ across cognitive tasks (as evidenced by the lack of significant Covid x

Table 3
COVID-19 Differences in Visual Analogue Mood Scale Ratings.

	COVID-19 Infection History							
	Non-Covid (n = 19)			Covid (n = 75)				
	M	SD	95 % CI	M	SD	95 % CI	p-value	BF_{10}
Sad	16	20	7–25	16	17	12–20	0.444	0.272
Energetic	43	15	36–50	45	21	40–49	0.351	0.270
Tense	24	19	15–32	37	23	32–42	**0.010**	**2.390**
Happy	54	19	46–63	60	15	56–63	0.102	0.398
Tired	55	19	46–63	58	22	52–63	0.324	0.366
Calm	71	21	61–80	63	20	59–67	0.065	**1.286**

Note. M = Mean; SD = Standard Deviation; Bolded text represents a significant group difference ($p < 0.05$) or anecdotal evidence in favour of the hypothesis ($1.0 < BF_{10} < 3.0$).

Table 4
Prefrontal Haemodynamic Response Analysis of Variance (n = 75 Covid and 19 Non-Covid).

	Δoxy-Hb		Δdeoxy-Hb		Δtotal-Hb	
Predictor	F	p-value	F	p-value	F	p-value
Covid	**8.292**	**.004**	**17.923**	**< .001**	**16.240**	**< .001**
Hemisphere	**5.050**	**.025**	3.157	.076	**15.466**	**< .001**
Task	**9.395**	**< .001**	**3.598**	**.001**	**6.153**	**< .001**
Covid x Hemisphere	**8.465**	**.004**	**24.259**	**< .001**	**19.558**	**< .001**
Covid x Task	0.229	.978	0.303	.953	0.039	1
Hemisphere x Task	0.038	1	0.087	.999	0.052	1
Covid x Hemisphere x Task	0.053	1	0.065	1	0.066	1

Note. Type III Sum of Squares. Bolded text represents a significant effect of the predictor on ΔHb ($p < .05$).

Hemisphere x Task interactions). Note that controlling for handedness and including mood variables as covariates in the model summarised in Table 4 resulted in no detectable moderating effects and identical statistical inferences.

Fig. 3 illustrates the significant Covid x Hemisphere interactions, and post-hoc analyses run with Tukey's correction revealed that the interaction for Δoxy-Hb (shown in panel A) was driven by a significant mean difference between the left and right hemisphere in the covid group (MD = -0.837, t = -5.704, d = -0.332, $p < 0.001$) but not in the non-covid group (MD = 0.107, t = 0.371, d = 0.043, p = 0.983), and a significant mean difference between groups in the right (MD = -0.940, t = -4.093, d = -0.372, $p < 0.001$) but not the left hemisphere (MD = 0.005, t = 0.021, d = 0.002, p = 1.000). Despite small visual differences, the same pattern of significant mean differences were observed to be driving the Covid x Hemisphere interaction for Δtotal-Hb (shown in Fig. 3C) with a significant mean difference between the left and right hemisphere in the covid group (MD = -1.338, t = -5.507, d = -0.320, $p < 0.001$) but not in the non-covid group (MD = 1.039, t = 2.167, d = 0.249, p = 0.133), and between groups in the right (MD = -2.272, t = -5.977, d = -0.543, $p < 0.001$) but not the left hemisphere (MD = 0.106, t = 0.278, d = 0.025, p = 0.993). As per Δoxy-Hb and Δtotal-Hb, the mean difference in Δdeoxy-Hb (shown in Fig. 3B) between groups was significant in the right (MD = -1.333, t = -6.476, d = -0.589, $p < 0.001$) but not the left hemisphere (MD = 0.101, t = 0.489, d = 0.044, p = 0.962). However, there were not only significant mean differences in Δdeoxy-Hb between hemispheres in the covid group (MD = −0.501, t = -3.811, d = -0.222, $p < 0.001$), but also in the opposite direction for the non-covid group (MD = 0.932, t = 3.590, d = 0.412, p = 0.002).

A follow-up MANOVA comparing those with subjective cognitive decline (brain fog) in the covid group with the non-covid controls

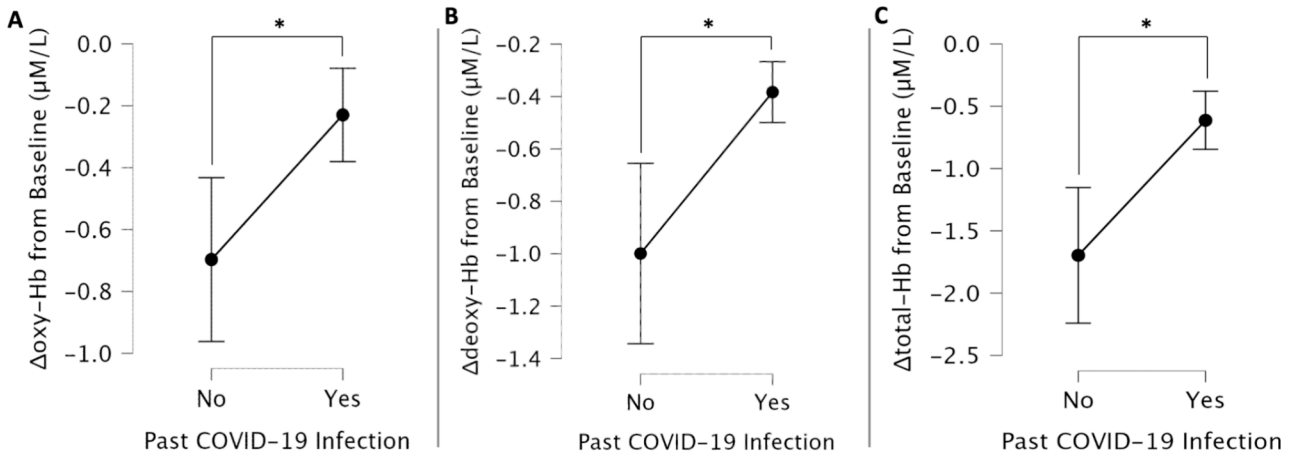

Fig. 2. Main Effect of Past COVID-19 Infection on Prefrontal Haemodynamic Response (n = 75 Covid and 19 Non-Covid). Note. Error bars represent 95 % confidence intervals.

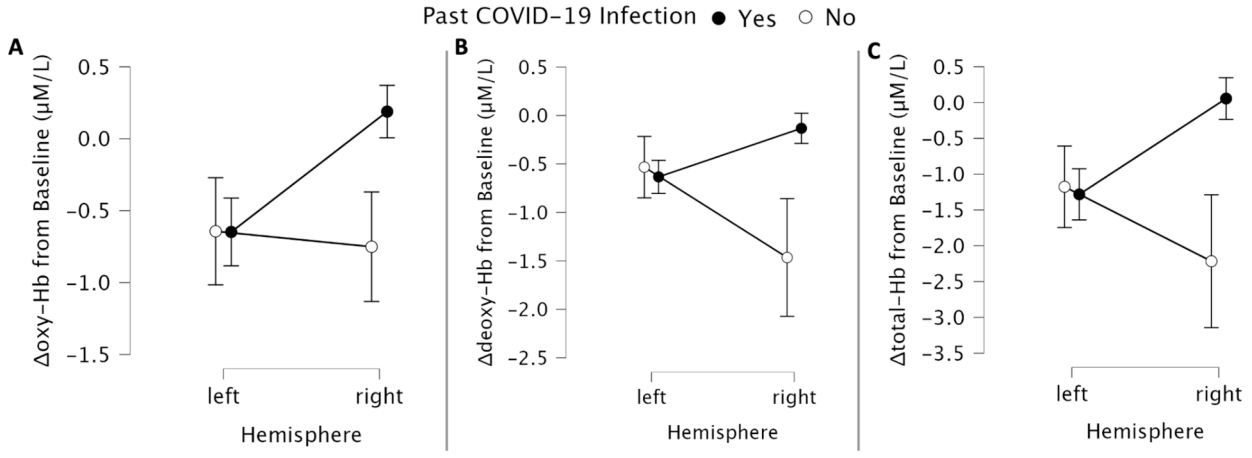

Fig. 3. COVID-19 x Hemisphere Interactions in Prefrontal Haemodynamic Response (n = 75 Covid and 19 Non-Covid). Note. Error bars represent 95 % confidence intervals.

(presented in Table S14) revealed the same pattern of effects to those presented in Table 4, except there was no significant effects of hemisphere, and the group x hemisphere interaction was not significant for Δoxy-Hb. Though underpowered, this analysis (visualised in Fig. S4) depicts that undergraduate students with a past COVID-19 infection and reports of subjective cognitive decline, exhibited a numerically more positive/less negative haemodynamic response (in line with the full covid group analysis). In the case of oxygenated haemoglobin, this pattern was observed irrespective of hemisphere, suggesting a less asymmetric difference compared to the full COVID group.

6. Discussion

Few studies have examined the prolonged neuropsychological effects of COVID-19 infection in undergraduate students, and to the best of our knowledge, this is the first study to measure cognitive task-related brain haemodynamic response differences post COVID-19 infection using NIRS. In support of our hypotheses, 37.33 % of participants who reported previously having COVID-19 displayed objective cognitive impairment and 40 % reported experiencing subjective cognitive impairment. However, on average, the covid group did not perform worse on the cognitive tests than the non-covid group. In support of our second hypothesis, participants in the covid group, during completion of cognitive tasks, exhibited less negative changes in oxygenated haemoglobin supply to the anterior prefrontal cortex. Interestingly though, the effect was specific to the right hemisphere, except when focusing in on those who reported brain fog (subjective cognitive impairment) due to COVID-19.

6.1. COVID-19 infection and neuropsychological function

Our objective cognitive performance findings are partially consistent with previous research objectively measuring long term cognitive impairment following COVID-19 infection. In the most recent investigations, cognitive impairment was also apparent in individual-level analyses among a proportion of previously infected participants (for comparison, 40 % in Henneghan et al., 2022, and 85 % in Herrera et al., 2023), and as per our study, group-level differences were not significant (Henneghan et al., 2022). In contrast, the initial research in this area found significant group-level cognitive impairment (Hampshire et al., 2021; Raman et al., 2021; Zhou et al., 2020). In recent years we have seen several waves of genetic mutations on the SARS-CoV-2 virus (Saha et al., 2021), which is one of the unmeasured potential confounds behind these scientific inconsistencies.

Cognitive difficulties following COVID-19 infection appear to be long lasting. In the current study, impairment was observed up to 17 months post-infection, aligning with previous research in young adults, where impairments persisted for up to 10 months following COVID-19 (Henneghan et al., 2022). Additionally, when analysed at the individual level in the present study, performance in the anti and pro/anti tasks (included to measure the executive functions inhibitory control and task switching abilities) was impaired most commonly. Notably, executive functions were also the most prevalent impairments observed in past studies (Henneghan et al., 2022; Herrera et al., 2023), indicating that difficulties in executive functioning following COVID-19 may be of particular concern. However, given the cross-sectional nature of these studies we cannot decipher if some undergraduate students were fully resilient to cognitive difficulties post infection, or whether they had cognitive difficulties that recovered by the time of testing. Nevertheless, the findings of the current study suggest that there is large individual variability in the cognitive effects of COVID-19 infection. This may reflect the ability of some students to successfully adapt or compensate for any neuropathogenic effects of COVID-19, allowing them to display preserved (or recovered) cognitive function. In relation to this, we also presented anecdotal evidence that more recently infected participants had a greater tendency to exhibit objective cognitive impairment. Variability in the rate of neuropsychological recovery between individuals, and other individual differences, may render group-level analyses of cognitive impairment ineffectual.

Interestingly, participants in the covid group were observed to be significantly more tense and anecdotally less calm during neuropsychological testing than those in the non-covid group. However, it should be noted that a numerically greater percentage of females in the covid group could have contributed to these observations given previously established sex differences in tense ratings among undergraduate students using the same VAMS (Machado et al., 2019). Regarding potential sex differences related to (objective) cognitive impairment, some past studies have suggested that females may be more susceptible to enduring neuropsychological effects of COVID-19 infection (Sylvester et al., 2022). Unfortunately, in the covid group of the current study very few males participated ($n = 7$); however, given the poverty of relevant data available, we nonetheless checked for sex differences in subjective and objective cognitive impairment and haemodynamic response and found no statistically significant effects (Tables S15 and S16). Given the extent to which these analyses were underpowered, future research will be needed to properly investigate this important topic.

6.2. COVID-19 infection and prefrontal haemodynamics

In an effort to shed some light on the neuropathogenesis of cognitive impairment in COVID-19, our study indirectly explored the microglial hyperactivation theory, presenting novel evidence of distinct haemodynamic patterns during cognitive tasks following COVID-19 infection. These patterns indicate comparatively greater prefrontal neuronal and/or microglial activation (Ayaz et al., 2019; Yang & Dunn, 2015). The negative change during cognitive testing shown in the non-covid group and in the left hemisphere of the covid group aligns with previous reports in undergraduate students (Cameron et al., 2015; Bierre et al., 2017); however, the right hemisphere of the covid group did not show this negative change. This may indicate microglial hyperactivation, theoretically driven by elevated oxidative stress from dysfunctional mitochondria—a possible contributor to cell death and cognitive impairment (Aghajani Mir, 2023). The pattern observed in the right hemisphere of the covid group may also indicate relatively greater neuronal activity within (the sampled) anterior prefrontal cortex. This pattern seems more in line with that observed bilaterally in healthy older adults aged 60–72 years (on average 46 years older; Bierre et al., 2017), who tend to recruit more anterior frontal regions not typically recruited in young adults (Bierre et al., 2017; Machado, 2021). The haemodynamic patterns observed here indicate that, in comparison to controls, post COVID-19 undergraduate students may exhibit hyperactivated microglia and neurons, as is typical in older adults (Edler et al., 2021).

We had not predicted that neurophysiological changes following COVID-19 infection would be restricted to the right hemisphere (based on the full covid group analysis). While unexpected, we note that hemispheric asymmetries are found across many neuropsychological disorders (Mundorf & Ocklenburg, 2021) and previous COVID-19 research has reported brain changes confined to the right hemisphere. Specifically, in comparison to controls, Cecchetti et al. (2022) found white matter hyperintensity volume differences in recovered hospitalised COVID-19 patients (mean age 59 years, $SD = 13$) in right but not left frontal regions. Additionally, Wu et al. (2024) reported increased prevalence of cognitive impairment in recovered COVID-19 patients with reduced glymphatic system activity, particularly in the right hemisphere, implicating altered glial cell function as a cause of the cognitive impairment (Roddy & van der Werf, 2020). These findings imply that long-term neurophysiological symptoms of COVID-19 infection tend to be localised to the right hemisphere. We theorise that the blood brain barrier may serve as a mechanism of asymmetric entry for pathogens into the brain, given evidence that cerebral blood flow is asymmetric, with the right hemisphere receiving greater flow (Risberg

et al., 1975), which may leave the right hemisphere more vulnerable to neuropathological effects following infection. However, in those who reported experiencing brain fog, the oxygenated haemoglobin response tended to be numerically more positive/less negative irrespective of hemisphere, suggesting that participants who reported brain fog were particularly impacted.

6.3. Limitations/future research

The homogeneity of the sample, predominantly female psychology students from the same university, may limit the generalisability of these findings. Hence, future research in a diversity of samples/contexts is needed to more broadly inform. Additionally, the non-covid group not only had a small sample size, but it is possible that some of these participants may have also had COVID-19 (e.g., they may have been asymptomatic or opted to abstain from testing). Furthermore, social isolation due to the COVID-19 pandemic has been linked to impaired cognitive function (Ingram et al., 2021), thus cognitive performance in the current study may be atypical irrespective of group, given New Zealand government mandates that required home isolation for at least 70 days (Department of the Prime Minister and Cabinet, 2024). Supporting this, both the covid and non-covid groups in the current study performed numerically worse on every cognitive measure compared to pre-pandemic students from the same university (White et al., 2018). Moreover, although participants likely had limited prior exposure to psychological experiments, some may have been familiar with similar cognitive tests, which, despite practice trials, could have influenced their performance, potentially diminishing our ability to detect adverse effects of COVID-19. With regard to these concerns, the prevalence of impairment observed in the current study was on the lower end of that observed in past research (Henneghan et al., 2022; Herrera et al., 2023). This may be due to a combination of the non-covid group being impaired and inflated variance metrics given the small sample size ($n = 19$). Variability in adherence to covid-related safety measures and testing frequency may have further contributed. Furthermore, no multiple comparison correction was applied to individual-level analyses; while this approach reduces risk of a Type II error, it elevates risk of a Type I error.

Future research may benefit from including lockdown duration/social isolation and adherence to safety measures as covariates in analyses. Additionally, given that individual level cognitive analyses indicated that COVID-19 may impair cognitive functioning in some but not all undergraduates, exploring sociodemographic and lifestyle factors may help identify undergraduates most at risk of cognitive impairment post-infection. Future research will also want to consider the changing variants of SARS-CoV-2, as the degree and nature of cognitive impairment may be influenced by the variant. Of particular importance, the use of NIRS as a single neuroimaging tool in the current study prevented distinction between neuronal versus glial causes of the haemodynamic differences. To address this limitation, positron emission tomography (PET) imaging using the benzodiazepine receptor ligand (R)-[11C] PK11195 can be used to measure differences in microglial functioning more directly (Edler et al., 2021), thus providing firmer evidence in relation to the microglial hyperactivation theory of cognitive impairment following COVID-19 infection. Additionally, the unique haemodynamic signature of microglia and astrocyte activity was recently proposed as detectable using diffusion magnetic resonance imaging (Garcia-Hernandez et al., 2022). Further research is needed to assess if glial and neural activity can be distinguished using NIRS.

7. Conclusions

The present study found evidence suggesting that COVID-19 infection is associated not only with subjective cognitive impairment but also with prolonged objective cognitive impairment, especially in executive functioning, in some but not all undergraduate students. Moreover, we found novel evidence of distinct task-related anterior prefrontal haemodynamic responses in students reporting a past COVID-19 infection relative to those reporting no past infection, and exploratory analyses suggested this may be particularly true for those who reported experiencing brain fog due to COVID-19. This new information may prove important as we move forward towards developing interventions in response to the mounting evidence that COVID-19 has prolonged influences on brain health. In closing, we call for scientists to respond urgently to the rapidly increasing prevalence of long covid symptoms pertaining to the brain.

Ethical considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the University Human Ethics Committee (reference code 22/020).

CRediT authorship contribution statement

Ronan McNeill: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rebekah Marshall:** Data curation. **Shenelle Anne Fernando:** Data curation. **Olivia Harrison:** Writing – review & editing. **Liana Machado:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2024.12.002.

Data availability

Data will be made available on request.

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